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A severe congenital myasthenic syndrome with "dropped head" caused by novel MUSK mutations

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Abstract: INTRODUCTION: Congenital myasthenic syndromes are rare. Mutations in MUSK were first described in 2004. Thirteen patients have been reported to date, mostly with a relatively mild course. The molecular diagnosis has implications for choice of treatment and genetic counseling. METHODS: Clinical course and electrophysiological, pathological, and genetic findings were assessed. RESULTS: We describe the case of a boy with prenatal onset and severe respiratory symptoms with a persisting need for ventilation. The patient had severe bulbar symptoms, marked axial weakness causing a "dropped head," and some facial and proximal weakness. Ophthalmoparesis developed during the first year of life. Salbutamol led to improvement, 3,4-diaminopyridine had a modest effect, but pyridostigmine produced deterioration. Two novel mutations in MUSK were found by whole exome sequencing. CONCLUSIONS: We expand the phenotype of congenital myasthenic syndromes with MUSK mutations, describing a more severe clinical course with prenatal onset. Predominant bulbar and respiratory weakness with facial and axial weakness and ophthalmoparesis are diagnostic clues.

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A SEVERE CONGENITAL MYASTHENIC SYNDROME WITH “DROPPED HEAD” CAUSED BY NOVEL *MUSK* MUTATIONS

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ABSTRACT: *Introduction:* Congenital myasthenic syndromes are rare. Mutations in *MUSK* were first described in 2004. Thirteen patients have been reported to date, mostly with a relatively mild course. The molecular diagnosis has implications for choice of treatment and genetic counseling. *Methods:* Clinical course and electrophysiological, pathological, and genetic findings were assessed. *Results:* We describe the case of a boy with prenatal onset and severe respiratory symptoms with a persisting need for ventilation. The patient had severe bulbar symptoms, marked axial weakness causing a “dropped head,” and some facial and proximal weakness. Ophthalmoparesis developed during the first year of life. Salbutamol led to improvement, 3,4-diaminopyridine had a modest effect, but pyridostigmine produced deterioration. Two novel mutations in *MUSK* were found by whole exome sequencing. *Conclusions:* We expand the phenotype of congenital myasthenic syndromes with *MUSK* mutations, describing a more severe clinical course with prenatal onset. Predominant bulbar and respiratory weakness with facial and axial weakness and ophthalmoparesis are diagnostic clues.

Muscle Nerve 52: 668–673, 2015

Congenital myasthenic syndromes (CMS) are rare genetic conditions affecting genes that code for proteins involved in neuromuscular transmission. So far, 20 causative genes have been identified,^{1–4} including genes that code for the acetylcholine receptor subunits *CHRNE*, *CHRNA1*, *CHRNA1*, *CHRNA1*, *CHRNA1*, *CHRNA1*, and *CHRNA1*, and the intracellular proteins RAPSIN and DOK7. Mutations in *MUSK* [the gene that codes for muscle-specific tyrosine kinase (MuSK)] are very rare. The first description was published 2004 by Chevessier *et al.*,⁵ and since

then only 10 different *MUSK* mutations in a total of 13 patients have been described (7 missense mutations, 7 small single-basepair indels, and a 2-exon deletion).^{5–10} The main clinical features described were facial and bulbar weakness, ptosis, and external ophthalmoplegia in most cases; respiratory problems, such as respiratory failure at birth or with respiratory infections, or neonatal stridor; and proximal and axial weakness with fatigability on walking. The further clinical course was generally described as mild, except for 1 patient who had a severe course with neonatal onset, respiratory failure, vocal cord paralysis, and need for tracheostomy. He died at 1.5 years of age.⁵ All other patients were able to walk. Respiratory problems were reported mostly in infancy, except for 1 patient who still needed nocturnal ventilation at age 19 years.⁸ Patients were reported to respond to salbutamol^{6,8} or 3,4-diaminopyridine,^{5,7} but there was no or only a temporary response to pyridostigmine or ephedrine.

We describe the case of a boy with prenatal onset and a severe clinical course, which expands the previously described phenotype. Using whole exome sequencing, 2 novel deleterious compound heterozygous mutations in *MUSK* were detected.

CASE REPORT

At his last visit the patient was a 4-year-old boy who was born at term to a non-consanguineous German couple. During pregnancy, polyhydramnios and bilateral club feet were noted at 23 weeks gestation without evidence of maternal diabetes.

At birth he presented with respiratory failure and was intubated. He had *pes equinovarus* on the left, a flat foot on the right, and bilateral hip dysplasia. He subsequently needed tracheostomy, as bilateral vocal cord palsy was also diagnosed. Weaning from mechanical ventilation was not possible

Abbreviations: CMS, congenital myasthenic syndromes; WES, whole exome sequencing

Key words: congenital myasthenia; dropped head; *MUSK*; ophthalmoparesis; respiratory weakness

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The first 2 authors (M.L.G. and P.J.) contributed equally to this study.

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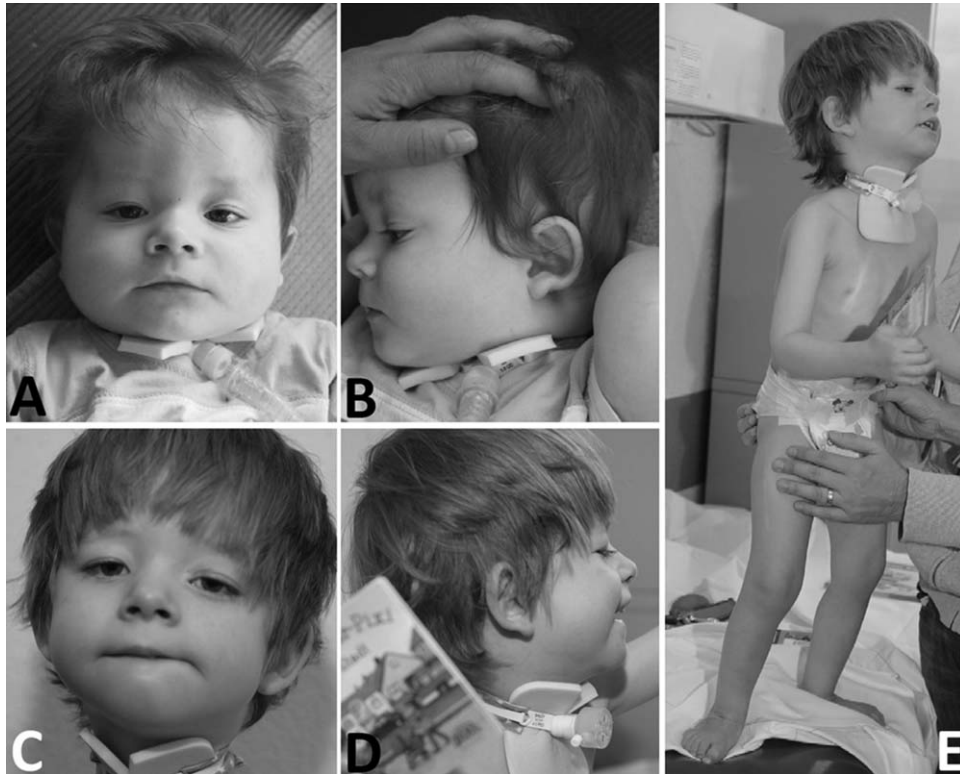


FIGURE 1. Clinical pictures of the patient at age 9 months (**A, B**) and at 3 years (**C–E**). Note the changing facial phenotype with normalizing ear lobe position but persistent poor head control.

due to repeated respiratory crises. In addition to the prominent respiratory problems there was axial muscle hypotonia, but he retained good antigravity movements of the legs more than the arms. Muscle biopsy showed variability of fiber size and type 2 fiber predominance. Because of the bilateral vocal cord palsy, a CMS was considered. At age 3 months, a test dose of pyridostigmine was given, which led to bradycardia and respiratory crisis and was therefore stopped. At 9 months, bilateral ptosis, external ophthalmoplegia, and some facial weakness were first noted. He had minor facial dysmorphism with uplifted ear lobes, hypoplasia of the supraorbital ridges, deep-set eyes, infraorbital creases, and bilateral single palmar creases with increased white lines (Fig. 1). A possible myasthenic syndrome was re-evaluated, and treatment with salbutamol liquid 3×0.15 mg/kg was started. This led to marked improvement in respiration, and weaning to a home ventilator was possible.

Stimulated single-fiber electromyography^{11,12} at 13 months showed increased jitter [average mean consecutive difference (MCD) was $69 \mu\text{s}$ (normal 26), no blocking].

This also indicated a disorder of neuromuscular transmission, although 3-Hz repetitive stimulation of the facial nerve did not show decrement. Motor development was delayed, but steadily improved. At age 2.5 years, he was able to stand up

without help and started walking. At 4 years he could climb stairs. He had marked facial and axial weakness leading to a “dropped head” and had moderate, predominantly proximal, muscle weakness affecting arms more than legs (Fig. 2). Clear fatigability was only noted after age 3. Marked swallowing problems have persisted from birth. Despite treatment, only small amounts of oral feeding are currently possible, and he is fed via gastrostomy. Mechanical ventilation is still necessary, although mainly during sleep at night and continuously during infections. The vocal cord palsy persists. *Pes equinovarus* resolved with physiotherapy. At 4 years he had a rigid spine but no scoliosis. Speech and cognitive development were normal.

In addition to the neuromuscular problem, brain MRI demonstrated a lesion in the left middle cerebral artery territory, which was attributed to perinatal hypoxic/ischemic injury leading to minimally increased muscle tone in the right leg.

Sanger sequencing of *DOK7*, investigated because of the response to treatment and stridor, *COLQ* because of the response to treatment and respiratory difficulties, and *CHRNE*, investigated because of the striking ophthalmoplegia, did not show pathogenic variants. Whole exome sequencing revealed compound heterozygous mutations in the *MUSK* gene [c.308A>G/= (p.Asn103Ser/=), exon 3; c.496C>T/= (p.Arg166*/=), exon 5,



FIGURE 2. Clinical pictures of the patient at 4 years of age. Note the “dropped head” posture.

both novel and each inherited in trans from each parent], establishing the final diagnosis.

After receiving the genetic diagnosis 3,4-diaminopyridine was added, and mild further improvement with increased stamina at a dose of 0.9 mg/kg/day was noted.

METHODS

Whole exome sequencing (WES) on genomic DNA extracted from peripheral blood lymphocytes of the patient was performed using a 70-Mbase genome-sequencing kit (SureSelectXT Human All-Exon V4+UTRs kit; Agilent Technologies) and with 65-bp forward and 30 reverse reads on another sequencing system (SOLiD 5500xl; ABI/Life Technologies). The average depth of coverage was 92×, and about 88% of the targeted bases were assessed by ≥ 6 independent sequence reads.

The candidate *MUSK* variants from WES were confirmed after polymerase chain reaction (PCR) amplification by Sanger sequencing using a genetic analyzer (ABI 3730; Applied Biosystems, Foster City, California).

The structural role of Asn103 was assessed based on the MuSK crystal structure (PDB code 2IEP).¹³ The Asn103Ser mutation was generated with Swiss-PDB Viewer,¹⁴ and RasMol¹⁵ was used for structural analysis and visualization.

Results of Mutational Analysis. WES in the patient revealed 2 heterozygous mutations within the coding region of the *MUSK* gene. One mutation located in exon 3 was a missense mutation affecting an evolutionarily highly conserved amino acid [c.308A>G/= (p.Asn103Ser/=)] and was predicted to be deleterious by 4 of 6 prediction tools applied (deleterious according to SIFT, PolyPhen, LRT, and Mutation Taster, tolerated according to Mutation assessor and FATHMM). The second mutation located in exon 5 was a stop mutation leading to premature truncation of the protein [c.496C>T/= (p.Arg166*/=)]. Both mutations were confirmed by Sanger sequencing and were shown to be compound heterozygous, as both parents, in addition to the wild-type, carried only 1 mutation each (Fig. 3). To further evaluate the functional effects, computational modeling of the mutant alleles on the protein structure was performed.

MuSK is a transmembrane protein containing a total of 5 domains. The extracellular N-terminus comprises 3 Ig-fold domains (residues 28–119, 121–208, 212–301) and 1 cysteine-rich domain (residues 317–448). The intracellular C-terminal part harbors the kinase domain (residues 575–856).

An Arg166* stop mutation thus lacks most of the extracellular domains as well as the kinase domain and is therefore expected to be catalytically inactive.

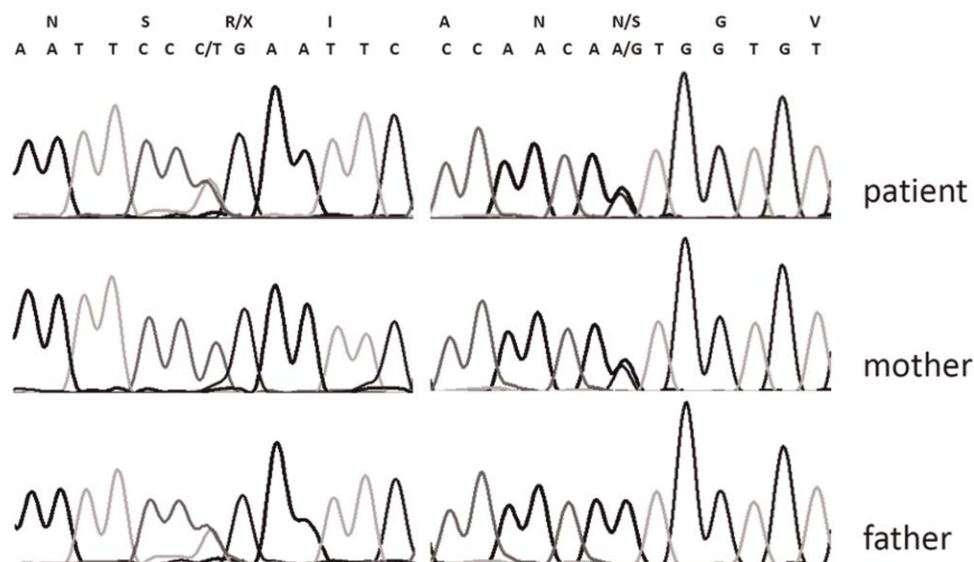


FIGURE 3. Partial electropherograms of the *MUSK* gene mutations in the patient and parents. This confirms compound heterozygosity for the mutations c.308A>G/= (p.Asn103Ser/=), in exon 3, and c.496C>T/= (p.Arg166*/=), in exon 5.

The Asn103Ser mutation is located in the first Ig-fold domain (Ig1), for which the crystal structure is known.¹³ Based on the predicted effect of the Asn103Ser mutation on Ig1 stability and the functional importance of this domain as an agrin binding site, it is expected that an Asn103Ser mutation would lead to severe functional impairment of MuSK (Fig. 4). In the wild type, the side chain of Asn103 forms a hydrogen bond to the backbone carboxyl group of Lys26, which is located at the very N-terminus of the Ig1 domain (Fig. 4A and B). Due to the shorter side chain of the serine, the respective hydrogen bond cannot be formed in the Asn103Ser mutant (Fig. 4C and D), which is expected to lead to significant destabilization of the N-terminus of the domain and may even cause unfolding of the entire domain. Previous experimental studies have demonstrated that the Ig1 is very sensitive to removal of stabilizing interactions. For example, the mutation of a non-canonical disulfide bridge in Ig1 results in improper folding and processing of MuSK.¹³

DISCUSSION

CMS with *MUSK* mutations are very rare. Until now, only 13 patients from 6 families have been reported. The reported phenotype in these patients comprises a lack of response to pyridostigmine, stridor/vocal cord palsy, and the need for ventilatory support, especially during the neonatal period and during infections. Furthermore, facial weakness, ptosis, and ophthalmoplegia are described commonly (10 of 13 patients). Six of the 13 patients had bulbar symptoms. The distribution of limb girdle weakness was reported as mostly proximal and axial. Onset in all patients was

before age 3 years, with neonatal onset in 6 patients, where reported.^{5–10}

We expand this phenotypic spectrum with a more severe and earlier prenatal onset; this includes polyhydramnios, contractures at birth, and severe respiratory and swallowing problems from birth, persisting at age 4 years. The distribution of weakness is similar to the reported cases with predominant axial and facial weakness, ptosis, and ophthalmoplegia, but with the weakness being more severe, leading to a “dropped head,” only partially ameliorated by treatment. As reported in other patients, he responded well to salbutamol and showed some further improvement with 3,4-diaminopyridine, but a pyridostigmine trial in infancy led to dramatic worsening.

We suggest that *MUSK* mutations be considered in patients with clinical suspicion of CMS with marked bulbar, respiratory, and axial weakness.

Severe congenital respiratory weakness, stridor due to bilateral vocal cord palsy, and bulbar weakness in the absence of marked weakness have also been described in patients with *DOK7* CMS.¹⁶ Other forms of CMS (*RAPSN*, *CHAT*, and fast-channel CMS) are also associated with early respiratory crises and bulbar weakness, but often weakness in these patients is more pronounced. Of note is that the development of external ophthalmoplegia and ptosis, which helps to distinguish from the phenotype described in *DOK7* patients, was delayed in the patient we have described.

The “dropped head,” as a sign of severe axial weakness, was a prominent feature in this patient. However, it is not specific for *MUSK*, having been described in other CMS and in congenital muscular dystrophies.^{17,18}

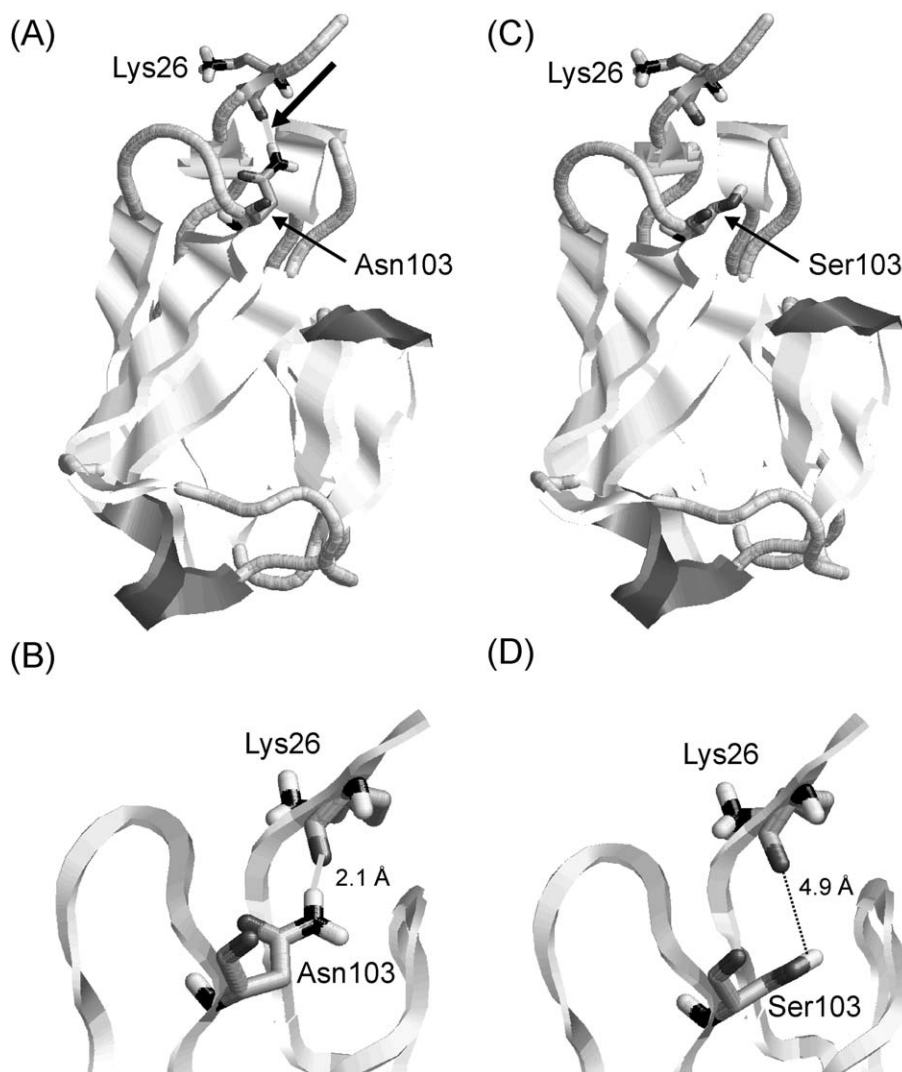


FIGURE 4. Effect of the Asn103Ser mutation on MuSK structure. **(A)** In wild-type MuSK, the side chain of Asn103 forms a hydrogen bond (bold arrow) to the backbone carboxyl group of Lys26. **(B)** Enlargement shows the interacting groups. The distance of 2.1 Å indicates the presence of a stable hydrogen bond. **(C)** Location of Ser103 in the Asn103Ser mutant. **(D)** Enlargement showing the relative orientation of Lys26 and Ser103. The distance of 4.9 Å between both residues (black dotted line) is too large for the formation of a hydrogen bond.

Orthopedic problems are seen quite often in the clinical course of *COLQ* patients, especially scoliosis.¹⁹ Scoliosis often develops in patients with *DOK7* mutations, but in the 13 patients with *MUSK* mutations from the literature, it was reported in only 1 patient.⁸ Our patient had *pes equinovarus* at birth, but it resolved with physiotherapy. He developed a rigid spine without scoliosis by age 4 years.

Repetitive nerve stimulation may fail to show decrement in CMS,²⁰ but stimulated single-fiber electromyography shows^{11,12} increased jitter. Electrophysiological investigations may be helpful for differentiation of CMS caused by mutations in *COLQ*, as in some patients with these mutations double compound muscle action potentials can be found after a single stimulus.¹⁹ CMS caused by mutations in *RAPSN* or *CHAT* and fast-channel syn-

dromes can also present with respiratory problems, but would be expected to show more generalized weakness and would respond well to pyridostigmine. It should be noted that testing for a response to pyridostigmine can be dangerous, as in some CMS it can lead to worsening or even acute life-threatening events, as seen in the patient described in this report.

Interestingly, patients with MuSK antibody-positive myasthenia also have more bulbar, respiratory, and axial muscle weakness than patients with antibodies against the acetylcholine receptor.²¹

In conclusion, CMS with *MUSK* mutations is very rare. Most patients reported to date have a relatively mild phenotype, but as shown here a more severe phenotype with prenatal onset is possible. Predominant bulbar and respiratory weakness with

later development of facial and axial weakness, a “dropped head,” and ophthalmoparesis may point to the diagnosis.

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MUSCLE MAGNETIC RESONANCE IMAGING ABNORMALITIES IN X-LINKED MYOPATHY WITH EXCESSIVE AUTOPHAGY

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ABSTRACT: *Introduction:* X-linked myopathy with excessive autophagy (XMEA) is an X-linked recessive myopathy due to recently reported mutations in the *VMA21* gene. *Methods:* Four men from 2 separate families were studied. The clinical presentation, genetic data, muscle biopsy, and muscle MRI were ana-

lyzed. *Results:* A known *VMA21* mutation, c.163+4A>G, and a new mutation, c.163+3A>G, respectively, were found in the 2 families. The clinical course was characterized by onset in childhood and progressive muscle weakness with a limb-girdle pattern. Muscle biopsy revealed a mild myopathy with an increased number of giant autophagic vacuoles. Whole-body muscle MRI showed that pelvic girdle and proximal thighs were the most and earliest affected territories, with sparing of rectus femoris muscles. Muscle changes essentially consisted of degenerative fatty replacement. *Conclusions:* This study highlights a distinctive MRI pattern of muscle involvement, which can be helpful for diagnosis of XMEA, even before muscle biopsy or genetic analysis.

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Abbreviations: AM, adductus magnus; BF, biceps femoris; CK, creatine kinase; EDL, extensor digitorum longus; GM, gluteus magnus; H&E, hematoxylin–eosin; LAMP-2, lysosome-associated membrane protein-2; OM, original magnification; PAS, periodic acid–Schiff; RF, rectus femoris; RYR1, ryanodine receptor 1; S, soleus; SM, semimembranosus; ST, semitendinosus; TA, tibialis anterior; VL, vastus lateralis; VM, vastus medialis; V-ATPase, vacuolar adenosine triphosphatase; XMEA, X-linked myopathy with excessive autophagy

Key words: excessive autophagy; muscle MRI; myopathy; *VMA21*; XMEA
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X-linked myopathy with excessive autophagy (XMEA) is a rare childhood-onset disease characterized by progressive vacuolation and atrophy of